EXHIBIT A86

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THE UTERINE PERISTALTIC PUMP

Normal and Impeded Sperm Transport within the Female Genital Tract

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1. SUMMARY

Rapid as well as sustained sperm transport from the cervical canal to the isthmical part of the fallopian tube is provided by cervico-fundal uterine peristaltic contractions that can be visualized by vaginal sonography. The peristaltic contractions increase in frequency and presumably also in intensity as the proliferative phase progresses. As shown by placement of labeled albumin macrospheres of sperm size at the external cervical os and serial hysterosalpingoscintigraphy (HSSG) sperm reach, following their vaginal deposition, the uterine cavity within minutes. In the early follicular phase a large proportion of the macrospheres remains at the site of application, while a smaller proportion enters the uterine cavity with even a smaller one reaching the isthmical part of the tubes. In the mid-follicular phase of the cycle with increased frequency and intensity of the uterine contractions the proportion of macrospheres entering the uterine cavity as well as the tubes has significantly increased. In the late follicular phase with maximum frequency and intensity of uterine peristalsis the proportion of macrospheres entering the tube increases further at the expense of those at the site of application as well as within the uterine cavity. The transport of the macrospheres into the tube is preferentially directed into the tube ipsilateral to the dominant follicle, which becomes apparent in the mid-follicular phase as soon as a dominant follicle can be identified by ultrasound. Since the macrosphere are inert particles the directed sperm transport into the tube ipsilateral to the dominant follicle is not

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functionally related to a mechanism such as chemotaxis but is rather provided by uterine contraction of which the direction may be controlled by a specific myometrial architecture in combination with an asymmetric distribution of myometrial oestradiol receptors.

Women with infertility and mostly mild endometriosis display on VSUP a uterine hyperperistalsis with nearly double the frequency of contractions during the early and mid- as well as midluteal phase in comparison to the fertile and healthy controls. During midcycle these women display a considerable uterine dysperistalsis in that the normally long and regular cervico-fundal contractions during this phase of the cycle have become more or less undirected and convulsive in character. Hyperperistalsis results in the transport of inert particles from the cervix into the tubes within minutes already during the early follicular phase, and may therefore constitute the mechanical cause for the development of endometriosis in that it transports detached endometrial cells and tissue fragments via the tubes into the peritoneal cavity. Moreover, dysperistalsis may contribute to the infertility in these patients since it results in a break down of sperm transport within the female genital tract.

2. INTRODUCTION

There is no doubt that the ultimate fate of the successful male germ cell is to impregnate the female oocyte, where its genetic material will fuse with that of the oocyte to result in fertilization and embryo formation. This particular sperm is usually deposited five to zero days prior to ovulation (Wilcox et al., 1995) in the posterior vaginal fornix in close vicinity to the external os of the cervical canal from where it reaches its final site of destination, the place of sperm-oocyte encounter within the tube ipsilateral to the dominant follicle.

Usually, the uterus is considered to be specialized, first, for the reception of the blastocyst by the endometrium and the continuous nourishment of the developing fetus and, second, for the eventual expulsion of the fetus (Romanini, 1994). Considering the fact that the sperm has to cover a long distance within the female genital tract from the external os of the cervix to the site of fertilization within the tube it is surprising that the facilitation and the guidance of this journey has only recently been considered a genuine and active function of the uterus (Kunz et al., 1996a). Previously, the ascension of the sperm within the female genital tract to the site of fertilization was regarded more or less a functional capacity of the sperm itself with the uterus serving merely as a passive canal, although a functional importance had been ascribed to uterine contractions (Moghissi, 1977; Harper, 1994). With respect to sperm ascension, attention was mostly directed towards the cervical canal with its glands and cyclically changing secretion. These are assumed to provide optimal conditions for the penetration of the sperm into the female genital tract around ovulation and serve, with its crypts, as a sperm reservoir, from where constant release for sustained sperm transport could occur. In this communication, the mechanism of uterine peristalsis will be discussed, and its role in sperm transport within the female genital tract will be outlined. It will be demonstrated that this function of the uterus is of fundamental importance in the process of reproduction and that disturbances of the uterine mechanism of sperm transport may result in infertility.

3. UTERINE PERISTALSIS

Rapid sperm transport from the vagina to the Fallopian tubes within minutes has been described in many species including man (Hartman, 1962; Mortimer, 1983; Hunter,

1987; Drobnis and Overstreet, 1992; Harper, 1994). Since the velocity of sperm movement does not itself account for covering such a long distance through the female genital tract within a few minutes, rapid sperm transport is considered a passive phenomenon and has been ascribed to uterine contractions (Moghissi, 1977; Harper, 1994; Kunz et al., 1996a; Leyendecker et al., 1996).

3.1. Vaginal Sonography of Uterine Peristalsis (VSUP)

Contractile activity of the non-pregnant uterus has been known for many decades (Hendricks, 1966; Cibils, 1967; Martinez-Gaudio et al., 1973). High resolution sonography has made it possible to demonstrate these contractions without invasive techniques. These contractions involve mostly the subendometrial layer of the myometrium and may be detected only by endometrial movements (Birnholz, 1984). Following their first description they have been further characterized (Oike et al., 1988; De Vries et al., 1990; Lyons et al., 1991; Fukuda and Fukuda, 1994). The contractions increase in frequency and in intensity as the follicular phase progresses with an inverse pattern during the luteal phase. The peristaltic waves of the endometrium and the subendometrial layer of the myometrium are directed from the cervical canal to the fundal part of the uterus, while only during menstruation do they exhibit a fundo-cervical direction (Lyons et al., 1991).

In our own study (Kunz et al., 1996a; Leyendecker et al.,1996), with measurements of the uterine peristalsis during the menstrual period, the early, mid- and late follicular as well as mid-luteal phases of the cycle, respectively (Fig. 1) it was demonstrated that there was a steady increase in peristaltic activity ranging from roughly 1.2 contraction per minute during the menstrual period and early follicular phase to 2.8 contractions per minute in the late follicular phase. During the mid-follicular and mid-luteal phases, respectively, the frequency averaged 1.5 contractions per min. Over the same time period, the proportion of fundo-cervical contraction waves decreased significantly from 43% during the menstrual period to less than 1% in the periovulatory phase. Thus, almost all peristaltic

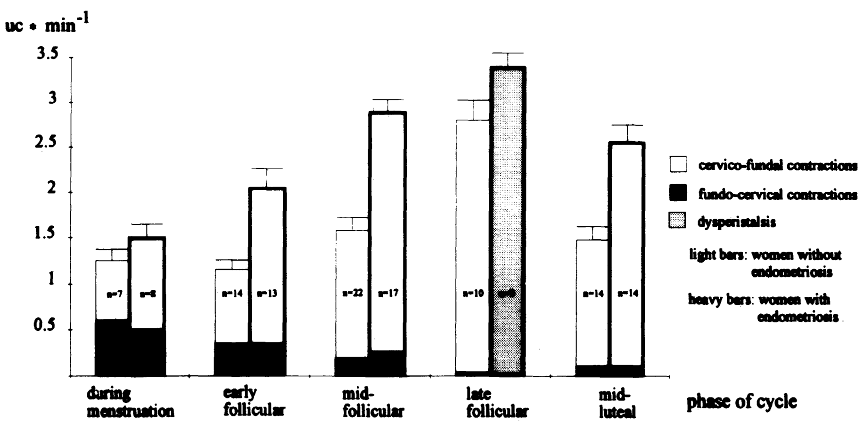


Figure 1. A graphical demonstration of the frequency of the subendometrial uterine peristaltic waves during menstruation, the early, mid- and late follicular and mid-luteal phases of the cycle, respectively, as determined by vaginal ultrasonography (contractions/min ± SEM). The graph shows also the relative distribution of fundo-cervical contractions versus cervico-fundal contractions during these different phases of the cycle (from Leyendecker et al., 1996).

waves of the uterus during the late follicular phase had a cervico-fundal direction. They also appeared to be more intense than during the other parts of the follicular phase, which might, however, be related to the thickness of the endometrium rendering the movements more pronounced. In comparison to the early follicular phase, however, a thicker proportion of the myometrium appeared also to be involved in the contractions. Because the frequency, intensity and direction of the uterine peristalsis depend upon the phase of the cycle, an endocrine control of this phenomenon by the ovary may be assumed. In this regard oxytocin and prostaglandins may function as mediators (Eliasson and Posse, 1960; Hein et al., 1973; Karim et al., 1973; Fuchs et al., 1985; Lefebvre et al., 1994a, Lefebvre et al., 1994b). This view is supported by the finding that administration of oestradiol valeriate to hypogonadal women yielding a pattern of serum oestradiol values similar to that of the normal cycle could completely mimic the cyclic changes of uterine peristalsis and that the frequency of the uterine peristaltic contractions could be significantly increased during the follicular phase of the cycle by the administration of an i.v. bolus of oxytocin. The increase in the frequency of the peristaltic contractions could be totally attributed to the peristaltic waves with cervico-fundal direction, which may be related to the high density of oxytocin receptors in the cervical tissue (unpublished).

Peristaltic contractions with the same frequency as described above were also observed with transvesical scanning (Birnholz, 1984). Thus, it is very unlikely that the uterine peristalsis was induced by the vaginal ultrasound examination. In contrast, it can be assumed that uterine peristalsis during the menstrual cycle is a continuous phenomenon with varying frequency, intensity and direction of the contraction waves depending on the phase of the cycle and does not require a specific stimulus for initiation. These studies, however, do not exclude a coital enhancement of uterine contractions.

3.2. Hysterosalpingoscintigraphy (HSSG)

It is reasonable to assume that the uterine peristaltic activity provides the forces that are required for the transport of spermatozoa from the external os of the cervix into the tubes within minutes. Using hysterosalpingoscintigraphy (Itturalde and Venter, 1981; Becker et al., 1988), rapid sperm transport was studied by placing technitium-labelled albumin macrospheres of sperm size at the external os of the uterine cervix and following their path through the female genital tract (Kunz et al., 1996a; Leyendecker et al., 1996).The albumin macrospheres used in our study resemble spermatozoa in their size. Thus, the demonstration of their ascension through the genital was considered to represent passive sperm transport.

According to these data (Fig. 2–4) the following concept of the dynamics of rapid sperm ascension within the female genital tract was proposed. Rapid sperm ascension occurs immediately following deposition of the ejaculate at the external os of the cervix. As early as one minute thereafter spermatozoa have reached the intramural and isthmical part of the tube. Quantitatively, however, the extent of ascension increases with the progression of the follicular phase. While only a few spermatozoa enter the uterine cavity and even fewer the tubes during the early follicular phase, the proportion of spermatozoa that enters the uterine cavity increases dramatically during the mid-follicular phase with still a limited entry into the tube. During the late follicular phase there is a considerable ascension of spermatozoa into the tubes.

Furthermore the HSSG revealed the preferential direction of rapid sperm transport into the tube ipsilateral to the dominant follicle. This corresponds with recent findings during surgery that the number of sperm around ovulation was higher in the tube ipsilat-

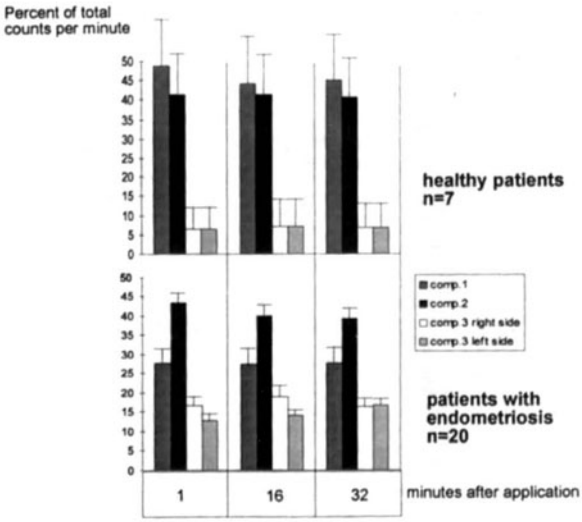


Figure 2. The distribution of the percentage of total counts, representing the labeled albumin macrospheres, within the female genital tract (compartment 1, 2 and 3 being the upper vagina, the uterine cavity and the isthmical part of the tubes respectively) following 1, 16 and 32 minutes after vaginal application during the early follicular phase. With respect to compartment 3, the right and left tubes were differentiated. The amount of radioactivity transported into the tubes was significantly higher in patients with endometriosis in comparison with healthy controls ($P< 0.01$) (from Leyendecker et al., 1996).

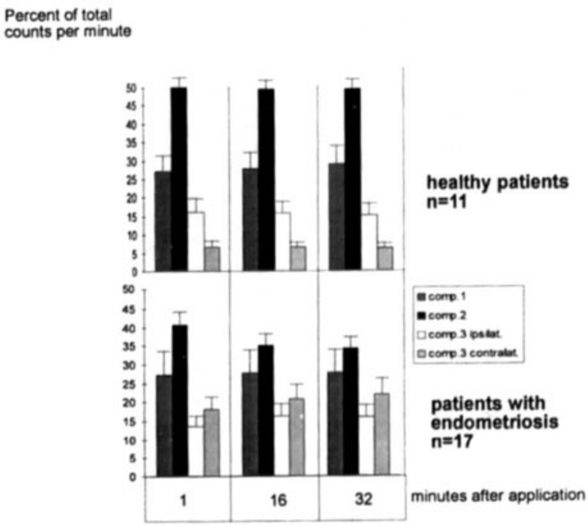
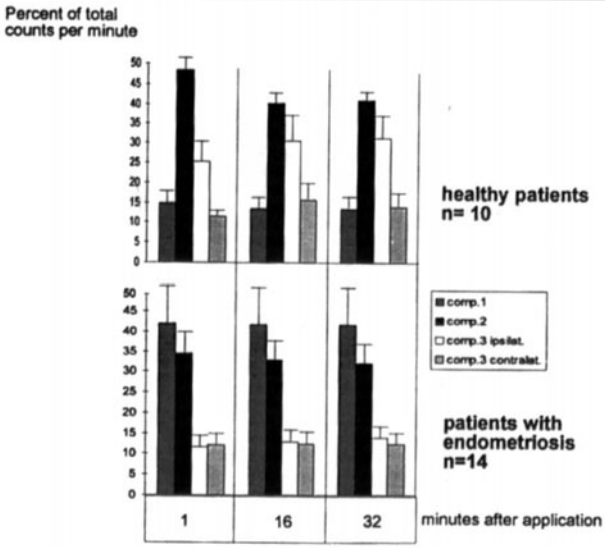


Figure 3. The respective distribution pattern of radioactivity, as in Fig. 2, obtained during the mid-follicular phase of the cycle. While in patients without endometriosis the labeled macrospheres preferentially entered the tube ipsilateral to the dominant follicle, in patients with endometriosis the macrospheres preferentially entered the tube contralateral to the dominant follicle. The difference in ascension into the contralateral tube between the two groups of patients was significant ($P<0.01$) (from Leyendecker et al., 1996).


Percent of total counts per minute
50
45
40
35
30
25
20
15
10
5
0
healthy patients
n= 10
comp.1
comp.2
comp.3 ipsilat.
comp.3 contralat.
patients with endometriosis
n=14
1
16
32
minutes after application

by the dominant follicle in that the uterine myometrium with its specific architecture (Goerttler, 1930) is activated and contracts in a manner providing this directed transport. In order to elucidate the mechanisms that govern directed sperm ascension, the estrogen receptor distribution within the myometrium was studied. It could be demonstrated in removed uteri that the percentage of estrogen receptor positive nuclei of smooth muscle cells in the myometrium was significantly higher on the side of the dominant ovarian structure in comparison with the contralateral side (Kunz et al., 1996b).

The strong correlation between receptor distribution and the site of the dominant ovarian structure suggested that the side-specific asymmetric estrogen receptor distribution is induced by the dominant follicle. This preferential induction of estrogen receptors in the myometrium on the side of the dominant ovarian structure is presumably not effected by the oestradiol concentration in the systemic circulation. Rather, it may involve a more direct endocrine influence mediated, for example, by the utero-ovarian vascular counter-current system (Einer-Jensen, 1988) that may provide higher oestradiol concentrations in the uterus on the side of the dominant follicle. This finding may also indicate that other hormone receptors in the uterus, pertinent to its contractile function, might be expressed asymmetrically with respect to the localization of the dominant ovarian structure. Preliminary data show that oxytocin receptors, exhibiting high concentrations in cervical tissue, like those for oestradiol, are asymmetrically distributed within the fundal part of the myometrium relative to the side of the dominant follicle (unpublished).

The asymmetric estrogen receptor distribution being presumably responsible for the directed sperm transport appears to be superimposed on a basal, more evenly distributed level of estrogen receptors under the influence of systemic oestradiol. This may be derived from the observation that the systemic administration of exogenous estrogen to hypogonadal women results in a uterine peristaltic activity which is, according to VSUP, indistinguishable from normal

5. UTERINE HYPERPERISTALSIS AND DYSPERISTALSIS

In studying infertile women suffering from mostly mild endometriosis, which is considered not to be a cause of infertility (Hull et al., 1986; Adamson and Pasta, 1994), a fundamental disturbance of uterine peristaltic activity was observed (Leyendecker et al., 1996) (Fig 1). In VSUP, these women displayed a considerable degree of hyperperistalsis in that, during the early and mid follicular as well as mid-luteal phase of the cycle, respectively, the frequency of peristaltic contraction was nearly doubled in comparison to normal. During the late follicular phase the frequency was increased further but less pronounced as compared to the early and mid-follicular phase of the cycle. The character of the peristaltic activity, however, had completely changed. While in the fertile controls long and regular cervico-fundal peristaltic waves prevailed, the contractions displayed a convulsive character in the infertile women. Some of the contraction waves started in the middle portion of the uterine cavity, while in other patients the contractions started at different sites at the same time, and some vanished before reaching the fundal part of the uterine cavity. Thus, in comparison with the regular and frequent cervico-fundal contractions of healthy women, the impression of a dysperistalsis prevailed in patients with infertility and endometriosis (Leyendecker and Kunz, 1996).

These abnormalities of the uterine peristaltic activity in women with endometriosis had a profound impact on the uterine transport function as demonstrated by HSSG, which, at least in part, may account for the infertility of these women. Already during the early

follicular phase of the cycle, there was a rapid transport of inert particles through the uterine cavity into the tubes. This was further increased during the mid follicular phase. However, there was no directed transport into the tube ipsilateral to the dominant follicle. During the late follicular phase, when the uterine contractions had become dysperistaltic, a breakdown of the uterine transport function occurred in that most of the particles remained at the site of application and only a few entered the tubes without a preference for the "dominant" one (Fig. 2–4).

6. IMPLICATIONS REGARDING THE FUNCTION OF THE CERVICAL MUCUS

These data are also pertinent in reconsidering some of the functions of the cervical mucus with regard to sperm ascension.. It is generally assumed that the sperm actively penetrate the cervical mucus and that the scant and viscous cervical mucus of the early follicular phase acts as a barrier in this respect (Moghissi, 1977). The HSSG demonstrates that already in the early follicular phase, in the presence of scant cervical mucus with little spinnbarkeit, a rapid transport of inert particles through the cervical canal occurs (Fig 2). Moreover, the distribution pattern of the labeled macrospheres within the genital tract of women with endometriosis and hyperperistalsis in the early follicular phase (Fig. 2; lower panel) resembles that of the healthy controls with normoperistalsis in the mid follicular phase of the cycle (Fig. 3; upper panel). Thus, it is not so much the quality of the cervical mucus but rather the power of the uterine peristalsis that determines the amount of sperm ascension through the cervical canal.

According to in vitro studies sperm penetrate the cervical mucus at a speed of 0.1 to 3 mm/min depending upon the phase of the cycle. There is no doubt on the basis of our studies that the sperm's own velocity is of little importance with respect to the ascension through the cervical canal. Irrespective of whether there is a function at all to the sperm's active movement at this stage of reproduction, the interaction of the sperm with the physico-chemical properties of the mucus enable viable sperm to enter the cervical crypts as a primary reservoir for later release. Of course, our model using inert albumin macrospheres cannot account for effects that have to be attributed to the functional capacity of healthy sperm.

7. AN INTEGRAL VIEW ON SPERM ASCENSION WITHIN THE FEMALE GENITAL TRACT AND ITS POSSIBLE DISTURBANCES

The clinician has been familiar for a long time with rhythmical contractions of the non-pregnant uterus. Upon cervical inspection during the preovulatory phase rhythmical protrusions of the abundant cervical mucus can be observed. Only recently, due to high resolution ultrasound examination, it was possible to relate these cervical activities to uterine peristaltic waves that originate in the cervix and are propagated towards the cornual section of the uterus. With the placement of labeled inert particles of sperm size at the external cervical os and following their path through the female genital tract by HSSG it was possible to demonstrate the enormous power and transport capacity of this uterine peristaltic pump. Furthermore, the directed transport of the particles preferentially into the

tube ipsilateral to the dominant follicle demonstrated the surprising sophistication of this uterine system of sperm transport (Kunz et al., 1996a).

On the basis of the data obtained in our studies and available from literature, we hypothesize that rapid as well as sustained sperm is controlled by uterine peristaltic activity. Uterine contractions aspirate sperm into the cervical mucus and the uterine cavity, and provide further transport into the isthmical part of the tubes. In the mid- and late follicular phases of the cycle this transport is directed preferentially into the tube ipsilateral to the dominant follicle. This indicates that the mechanism of rapid and passive sperm transport is under the endocrine control of the dominant follicle. Some sperm, probably the most motile ones, follow, by their own movement, the filamentous structures of the cervical mucus and enter the cervical crypts as a primary reservoir. This results in a partial sequestration of the sperm increasing the proportion of less motile and immobile sperm that reach the tubes rapidly. This observation has probably lead to the notion that rapid sperm ascension might not be essential for fertilization (Mortimer, 1983; Hunter, 1987). With the progression of the follicular phase there is an increasing release of sperm from the primary reservoir as they are flushed and squeezed out of the crypts due to the cervical secretion which becomes more profuse and the rhythmical contractions that originate within the cervix, respectively. Entering the "main stream" of cervical secretion they are caught by the "uterine peristaltic system" and rapidly transported in an aliquot of mucus (Fukuda and Fukuda, 1994), which protects the sperm from leukocyte degradation within the uterine cavity (Harper, 1994), to the tube with its isthmic mucus as the secondary reservoir. Dilatation of the external cervical os, maximum cervical secretion and rhythmical protrusion of the mucus around ovulation enlarge the zone of contact between a fresh ejaculate and the uterine peristaltic pump. At the same time preovulatory mucorrhea, together with the rhythmical contractions of the cervix, prevents by large motile sperm from entering the cervical crypts and thus ensures, in combination with maximally increased uterine peristalsis, that no or only minor sequestration of sperm can occur and that motile sperm are directly transported into the isthmical mucus (Jansen, 1980) of the tube ipsilateral to the dominant follicle where they are available for fertilization.

There is, in our opinion, no principle difference between the mechanisms of rapid and sustained sperm transport, respectively. Both aim at the availability of viable sperm at the site of fertilization around ovulation and both rely, in this respect, on the continuous peristaltic activity of the uterus. Sustained sperm transport utilizes the cervical crypts as a primary reservoir, from where later release occurs. The reduced power of the peristaltic pump several days prior to ovulation in comparison to the preovulatory phase might, together with a more viscous cervical mucus at this time, facilitate the migration of motile sperm into the cervical crypts. No data are available, which of the two reservoirs, the cervical or the tubal mucus, have a preponderance in the function of sperm preservation. If there is any preponderance at all, one may assume that it may shift from the cervix to the tube with the progression of the preovulatory phase. In any event, the fundamental importance of sperm preservation within the genital tract and sustained sperm transport for the overall process of reproduction is documented by the observation that intercourse several days prior to ovulation may result in a pregnancy with a considerable probability ranging from about 10% with intercourse five to more than 30% with intercourse two days prior to ovulation, respectively (Wilcox et al., 1995).

These data and considerations show that the availability of sperm at the site of fertilization at the appropriate time depends to a large extent on coordinated uterine peristaltic contractions that cyclically change in quality and frequency. At a low frequency and power, they may favor sperm preservation within the cervical mucus, at a higher preovula-

tory frequency and power of contractions, the uterine peristaltic pump provides rapid and directed transport of sperm either from the reservoir or from a freshly deposited ejeculate into the tube ipsilateral to the dominant follicle.

Recently, it could be shown that this fine-tuned system is fundamentally disturbed in women with infertility and, mostly, mild endometriosis. Both, the hyper- and dysperistalsis of the uterine peristaltic pump observed in these women may contribute to their reduced fertility. Hyperperistalsis may prevent the development of an adequate pool of preserved sperm within the reservoir of the cervical crypts, and preovulatory dysperistalsis impedes, by a breakdown of sperm transport, the formation of an adequate sperm reservoir in the mucus of the isthmical part of the tube from where sperm migrate to the final site of fertilization.

Independent of its effects on sperm transport and fertility uterine hyperperistalsis may promote the detachment and exfoliation of endometrial cells and tissue fragments and their transtubal transport into the peritoneal cavity and may, therefore, propagate the development of endometriosis (Leyendecker et al., 1996).

8. CONCLUSIONS

Uterine peristalsis is of fundamental importance in the process of reproduction in that it serves sperm transport from the external os of the cervix to the mucus of the isthmical part of the tube ipsilateral to the dominant follicle. This mechanism is controlled by the dominant follicle. This newly disclosed and described uterine function is of clinical importance in that a dysfunction of this functional system may result in infertility and may propagate the development of endometriosis.

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